New-onset atrial fibrillation in critically ill patients and its association with mortality: A report from the FROG-ICU study

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Abstract: BACKGROUND: Atrial fibrillation (AFib) is associated with adverse outcome in critical illness, but whether this effect is independent from other risk factors remains uncertain. New-onset AFib during critical illness may be independently associated with increased in-hospital and long-term risk of death. METHODS: FROG-ICU was a prospective, observational, multi-centre cohort study designed to investigate the outcome of critically ill patients. Inclusion criteria were invasive mechanical ventilation and/or treatment with a positive inotropic agent for >24 h. Heart rhythm was assessed at inclusion and during ICU stay with digital ECG recordings. Among patients who had AFib during ICU stay, new-onset and recurrent AFib were diagnosed in patients without and with previous history of AFib, respectively. Primary endpoint was in-hospital mortality; secondary endpoint was 1-year mortality among ICU survivors. RESULTS: The study included 1841 critically ill patients. During ICU stay, AFib occurred in 343 patients (19%). New-onset AFib (n = 212) had higher in-hospital mortality compared to no AFib (47 vs. 23%, P < 0.001) or recurrent AFib (34%, P = 0.032). New-onset AFib showed increased risk of in-hospital death after multivariable adjustment compared to no AFib (OR 1.6, P = 0.003) or recurrent AFib (OR 1.8, P = 0.02). Among the 1464 ICU-survivors, new-onset AFib during ICU stay showed higher post-ICU risk of death compared to no AFib (HR 2.2, P < 0.001). After multivariable adjustment, new-onset AFib showed higher post-ICU risk of death compared to no AFib (HR 1.6, P = 0.03). CONCLUSION: New-onset AFib is independently associated with in-hospital and post-ICU risk of death in critically ill patients.

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Disclosures

AR received lecture fees from Amomed Pharma GmbH and Orpha Swiss GmbH, which both distribute esmolol and vernakalant.

Keywords

Atrial fibrillation; ICU; critical illness; outcome; mortality

Abstract

Background

Atrial fibrillation (AFib) is associated with adverse outcome in critical illness, but whether this effect is independent from other risk factors remains uncertain. New-onset AFib during critical illness may be independently associated with increased in-hospital and long-term risk of death.

Methods

FROG-ICU was a prospective, observational, multi-centre cohort study designed to investigate the outcome of critically ill patients. Inclusion criteria were invasive mechanical ventilation and/or treatment with a positive inotropic agent for more than 24 hours. Heart rhythm was assessed at inclusion and during ICU stay with digital ECG recordings. Among patients who had AFib during ICU stay, new-onset and recurrent AFib were diagnosed in patients without and with previous history of AFib, respectively. Primary endpoint was in-hospital mortality; secondary endpoint was 1-year mortality among ICU survivors.

Results

The study included 1841 critically ill patients. During ICU stay, AFib occurred in 343 patients (19%). New-onset AFib (n=212) had higher in-hospital mortality compared to no AFib (47 vs. 23%, $P<0.001$) or recurrent AFib (34%, $P=0.032$). New-onset AFib showed increased risk of in-hospital death after multivariable adjustment compared to no AFib (OR 1.6, $P=0.003$) or recurrent AFib (OR 1.8, $P=0.02$). Among the 1464 ICU-survivors, new-onset AFib during ICU stay showed higher post-ICU risk of death compared to no AFib (HR 2.2, $P<0.001$). After multivariable adjustment, new-onset AFib showed higher post-ICU risk of death compared to no AFib (HR 1.6, $P=0.03$).

Conclusion

New-onset AFib is independently associated with in-hospital and post-ICU risk of death in critically ill patients.

Keywords: Atrial fibrillation; ICU; critical illness; outcome; mortality

Introduction

Atrial fibrillation (AFib) is the most common arrhythmia in critically ill patients with incidence up to 25% in non-cardio-surgical intensive care units (ICUs) [1,2]. In critically ill patients, AFib may precipitate acute heart failure and thromboembolic complications [3-5]. Critical illness may induce the development of AFib in patients without previous history of arrhythmia (new-onset AFib) or precipitate relapses in patients with history of paroxysmal AFib (recurrent AFib). The underlying mechanisms include fluid and electrolyte imbalance, inflammation, ischemia and adrenergic overstimulation [2], which impair efficacy of treatments and promote early relapses [6].

Several studies reported increased short-term mortality and longer hospital stay associated with development of AFib during critical illness [7,8], however, there is still uncertainty whether new-onset AFib is merely a marker of disease severity or independently contributes to unfavourable outcome. Two very recent studies provided opposing results. Gupta et al. failed to show independent association between the presence of AFib (new-onset or recurrent) during critical illness and in-hospital mortality [9]. By contrast, Shaver et al. described increased in-hospital mortality associated with new-onset or recurrent AFib, independently from the severity of critical illness or underlying cardiac risk factors [10].

Moreover, little is known about the impact of AFib, in particular new-onset forms, on outcome after recovery from critical illness. Neither Gupta et al. nor Shaver et al. reported on the long-term outcomes of their patients. Chen et al. recently identified new-onset AFib as independent predictor of 60-day mortality in medical ICU patients [11]. Previously, Meierhenrich et al. failed to show a difference in long-term mortality associated with AFib in septic shock patients [12].

The primary aim of this French and euRopean Outcome reGistry in Intensive Care Unit (FROG-ICU) sub-study was to test the hypothesis that new-onset AFib during critical illness is independently associated with in-hospital and post-ICU mortality.

Methods

Study design

The FROG-ICU study was a prospective, observational, multi-centre cohort study designed to investigate long-term mortality of critically ill adult patients [13]. All consecutive patients admitted to any of the 28 participating medical, surgical or mixed ICUs in 19 hospitals in France and Belgium were screened for eligibility. Inclusion criteria were invasive mechanical ventilation and/or treatment with a positive inotropic agent for more than 24 hours. Exclusion criteria were age less than 18 years, severe head injury, brain death or persistent vegetative state, pregnancy or breastfeeding, organ transplantation in the last 12 months and/or lack of social security coverage.

Heart rhythm was assessed continuously at the patient's monitor by the investigators and documented by digital 12-lead ECG at inclusion, during the first 3 days of ICU stay, twice a week thereafter and at ICU discharge. Concomitantly, patient characteristics including medical history, hemodynamic parameters and medical treatment were recorded. Details about study design have been previously published [13]. Patients with lacking information about heart rhythm were excluded from this sub-study. Figure 1 shows the flowchart of the study population.

Among patients who had any episode of AFib during ICU stay, new-onset and recurrent AFib were diagnosed in patients without and with previous history of AFib, respectively. Patients who remained in sinus rhythm were defined as "no AFib".

Primary endpoints was in-hospital mortality. Secondary endpoint was 1-year mortality among ICU survivors.

The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki 2002, validated by the corresponding ethical committees and registered on ClinicalTrials.gov (NCT01367093).

Statistical analysis

Continuous variables are expressed as median (interquartile range), nominal variables are expressed as number (percentages). Differences between independent groups were assessed with Wilcoxon rank sum test, Mann Whitney U test and Fisher's exact test, as appropriate. Adjusted P-values for multiple comparisons are reported, if appropriate. Unadjusted and covariate adjusted logistic regression models were used to determine the association between AFib and in-hospital mortality. Using step-by-step

backward regression, 7 independent covariates of in-hospital mortality (age, gender, Simplified Acute Physiology Score (SAPS II), treatment with inotropes or vasopressors at inclusion, serum lactate level at inclusion, high-sensitive troponin I at inclusion, B-type natriuretic peptide (BNP) at inclusion) were selected among 15 clinical variables with prognostic value on short-term outcome (age, gender, SAPS II, history of congestive heart failure, history of coronary artery disease, history of hypertension, history of diabetes, septic shock at inclusion, neurological disease at inclusion, treatment with inotropes or vasopressors at inclusion, serum lactate level at inclusion, serum creatinine at inclusion, BNP at inclusion, high-sensitive troponin I at inclusion, C-reactive protein (CRP) at inclusion). Risk of in-hospital mortality is expressed as odds ratio (OR) and 95% confidence interval (CI). Long-term survival was plotted with the Kaplan-Meier curve and difference between groups were tested with the log-rank test. Unadjusted and covariate adjusted Cox proportional hazards models were used to evaluate the association between AFib and one-year mortality in ICU survivors. Adjustments were performed for the previously identified 14 independent predictors of one-year post-ICU survival (age, Charlson comorbidity index, loss of autonomy, severe valve disease or prior valve surgery, chronic renal disease, peripheral vascular disease, recent malignant tumors, red blood cell transfusion during ICU stay, length of ICU stay > 20 days, systolic blood pressure at ICU discharge, body temperature at ICU discharge < 37°C, leucocytes at ICU discharge > 20 G/L, platelets at ICU discharge < 10 G/L, total serum protein at ICU discharge < 60 g/L) [14]. Risk of one-year mortality is expressed as hazard ratio (HR) and 95% CI. The null hypothesis was rejected with an adjusted two-sided *P*-value < 0.05. All statistical analyses were performed using R statistical software (The ”R” Foundation for Statistical Computing, Vienna, Austria).

Results

Study population and outcome

A total of 2087 patients were included in the FROG-ICU cohort from July 2011 to December 2013. Two-hundred and forty-six patients (12%) were excluded from the analysis because of lacking data about heart rhythm. The study population consisted of 1841 critically ill patients with a median Simplified Acute Physiology Score (SAPS II) of 49 (35-63) points (Figure 1). Supplemental Table 1 summarizes

baseline characteristics of the study population. The median delay between ICU admission and study inclusion was 3 (2-5) days. The median ICU length of stay was 13 (7-22) days. The ICU and in-hospital mortality were 20% and 26%, respectively.

Incidence of arrhythmia during ICU stay

AFib was documented in 343 patients (19%) during the ICU stay. By contrast, 1498 patients (81%) remained in sinus rhythm (no AFib). New-onset AFib and recurrent AFib were diagnosed in 212 and 131 patients, respectively. As depicted in Figure 2, the first episode of AFib mostly occurred the day of study inclusion, with decreasing incidence in the following days. Of the 1464 ICU survivors, ECG at discharge was available for 922 patients. AFib was documented in 90 patients (9.8%).

In-hospital outcome of patients with new-onset AFib

Patients with new-onset AFib had higher in-hospital mortality (47%) compared to patients with no AFib (23%, $P<0.001$) and recurrent AFib (34%, $P=0.032$), as illustrated in Figure 3. New-onset AFib and recurrent AFib were both associated with increased risk of in-hospital death compared to no AFib (OR 3.0 (95% CI 2.2-4.0), $P<0.001$) and OR 1.8 (95% CI 1.2-2.6), $P=0.004$), respectively). New-onset AFib was associated with higher risk of in-hospital death compared to recurrent AFib (OR 1.7 (95% CI 1.1-2.6), $P=0.024$).

Patients with new-onset AFib showed several notable differences in clinical and disease characteristics (Supplementary Table 1). After adjustment for 7 independent covariates of in-hospital mortality, new-onset AFib was independently associated with higher in-hospital risk of death compared to no AFib (OR 1.6 (95% CI 1.2-2.2), $P=0.003$) and to recurrent AFib (OR 1.3 (95% CI 1.01-1.8), $P=0.04$). Conversely, recurrent AFib showed similar risk of in-hospital death compared to no AFib, after adjustment for clinical confounders (OR 0.9 (95% CI 0.6-1.4), $P=0.70$), Figure 3.

Furthermore, median length of ICU stay of patients with new-onset AFib (15 (9-28) days) was longer compared to those of patients with no AFib (12 (7-21) days) or recurrent AFib (12 (8-21) days), $P=0.009$. Among ICU survivors, patients with new-onset AFib (14 (9-23) days) had still longer ICU stay compared to those with no AFib (12 (7-21) days) or recurrent AFib (12 (8-21) days), although the difference was not significant, $P=0.28$.

Post-ICU mortality of patients with new-onset AFib

A total of 1464 patients were discharged alive from ICU. As shown in Figure 4, ICU survivors with new-onset AFib during ICU stay (n=129) showed higher 1-year mortality compared to ICU survivors with no AFib (n=1232, paired log-rank *P*<0.001), but similar to ICU survivors with recurrent AFib (n=103, paired log-rank *P*=0.40*).*

After multivariable adjustment for 14 independent predictors of one-year post-ICU survival, ICU survivors with new-onset AFib showed higher 1-year risk of death compared to patients with no AFib (HR 1.6 (95% CI 1.1-2.4), *P*=0.030). Recurrent AFib was associated with no significant association with increased risk of death compared to patients with no AFib (HR 1.4 (95% CI 0.9-2.1), *P*=0.23), Figure 4.

Discussion

The present study shows that new-onset AFib is an independent predictor of in-hospital and long-term mortality in a large, international, multi-centre ICU population.

The management of critically ill patients developing AFib is challenging. Indeed, AFib may impair the ventricular filling and precipitate acute heart failure [3-5], on the other hand, management of AFib in ICU patients is particularly difficult, because many antiarrhythmic treatments are either contraindicated or their efficacy is reduced, predisposing to early relapses [6,15,16]. Understanding whether AFib independently contributes to worse outcome of critically ill patients or is merely a marker of disease severity is therefore of crucial importance. In fact, depending on whether AFib independently contributes to worse outcome (or not), further research may be needed to find strategies for reducing the burden of AFib in critically ill patients.

Our study confirmed a high prevalence of AFib in critically ill patients, previously shown in medical, surgical and cardio-surgical ICU settings [8,12,17-19]. Our data also confirmed that the incidence of AFib during ICU stay is particularly high in the first days of acute illness [7,8,18].

Our study showed that critically ill patients developing AFib during ICU stay, and in particular those with new-onset AFib, had higher in-hospital mortality compared to patients without AFib. This observation is

in line with previous data, showing worse short-term outcome in ICU patients with new-onset AFib compared to patients without or with recurrent AFib[7]. By adjusting for clinical confounders, the present study clearly shows the independent association of AFib with increased risk of in-hospital death. These results are in contrast with data from a retrospective single-centre study by Gupta et al. and a prospective multi-centre study by Annane et al., which both failed to show independent association of AFib with increased in-hospital mortality [8,9].

Multiple explanations exist for these contrasting results. First, both studies did not separately analyze new-onset and recurrent forms of AFib. Second, the study by Gupta et al. included a population of less severely ill patients compared to FROG-ICU with significantly lower physiologic derangements and in-hospital mortality. This may have reduced the detrimental effect of AFib on short-term mortality. Third, the study by Annane et al. did no distinction between AFib and other forms of supraventricular tachycardia. Furthermore, the relatively low number of events and the high number of covariates used for adjustment may have impaired the ability to see relevant associations between arrhythmias and in-hospital outcome.

Conversely, a recent prospective single-centre study by Shaver et al. identified AFib (either new-onset or recurrent) as independent predictor of in-hospital mortality in critically ill patients, as reported in our study[10]. In addition, our study showed an even higher risk of in-hospital death in patients with new-onset compared to those with recurrent AFib, regardless of illness severity. The reasons for this difference are unknown, but one might speculate that both the hemodynamic consequences and mortality associated with the presence of AFib during critical illness might be more dramatic in patients not “adapted” to the arrhythmia.

The present study further addressed the association of AFib during ICU stay and long-term risk of death. Raw survival data indicated that ICU survivors with either new-onset or recurrent AFib had higher long-term mortality compared to patients without AFib. However, only the presence of new-onset AFib during ICU stay did independently predict worse long-term outcome, while recurrent forms did not. This observation adds an important piece in the puzzle of knowledge about AFib during critical illness. Indeed, it delimitates the detrimental effect of AFib on survival of critically ill patients to the new-onset forms. A retrospective single-centre study by Chen et al. identified new-onset AFib as independent predictor of 60-day mortality in a medical ICU population [11]. A single-centre study by Meierhenrich et

al. including septic shock patients and a single-centre study by Topaz et including acute myocardial infarction patients, showed a trend toward higher long-term mortality in new-onset AFib compared to patients without AFib, although the differences were not statistically significant because of an underpowered studies [12,20]. The present study, using an international, multi-centre design and including a very large, tough well characterized, mixed ICU population describes new-onset AFib as an independent predictor of long-term risk of death in ICU patients, while recurrent AFib is rather a marker of comorbidity burden and secondarily to worse long-term outcome without independent association with increased long-term risk of death.

Limitations

Our study has several limitations that deserve to be acknowledged. Firstly, the study included adult critically ill patients in predominantly non-cardiac ICUs, and therefore the results may not be generalized to the paediatric and cardiac ICU population. Secondly, the presence of AFib was assessed by reviewing patient's chart and digitally recorded ECGs. Using this technique, although being standard in clinical practice, short and asymptomatic episodes of AFib might have been missed compared to using continuous Holter-ECG recordings [18]. Nevertheless, the prevalence of AFib in our cohort is in line with other studies, including those who used other techniques of detection [21]. However, misclassification of some AFib patients in the no-AFib group would have weakened our results, which conversely are strong and consistent. Moreover, study inclusion occurred after ICU admission. As a consequence, since ECG recordings prior ICU admission are not available, the group of patients with recurrent AFib includes patients with history of AFib developing AFib during hospital stay and those with pre-existing persistent or permanent AFib. Thirdly, due to the observational study design, management of patients with or without AFib, in particular concerning cardioversion and antiarrhythmic treatments, is not controlled and whether AFib itself or its treatment has led to the observed differences in outcome, is unknown. A recent study by Balik et al. showed that restoration of sinus rhythm was associated with better one-year outcome in univariate analysis, but restoration of sinus rhythm was not independently associated with better one-year outcome after multivariable adjustment, suggesting that successful restoration of sinus rhythm might be rather a "marker" of more favorable prognosis [22]. Moreover, since the majority of patients in our study were in sinus rhythm at ICU discharge, differences in outcomes cannot be attributed to lack of conversion in sinus rhythm. Additional studies to assess the impact of preventive

strategies or antiarrhythmic therapies on incidence of AFib and in-hospital outcome of critically ill patients are needed.

Fourthly, despite careful identification and selection of co-variables to adjust the risk of death associated with AFib, other hidden variables not included in the models may interfere with our results.

Conclusion

New-onset AFib, but not recurrent AFib, is independently associated with increased risk of in-hospital death and one-year outcome of ICU survivors in critically ill patients.

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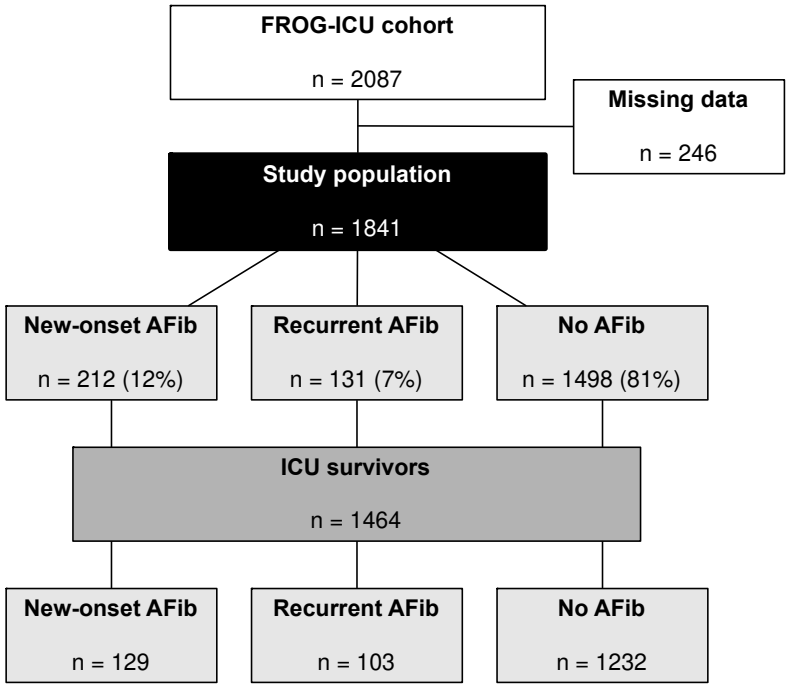
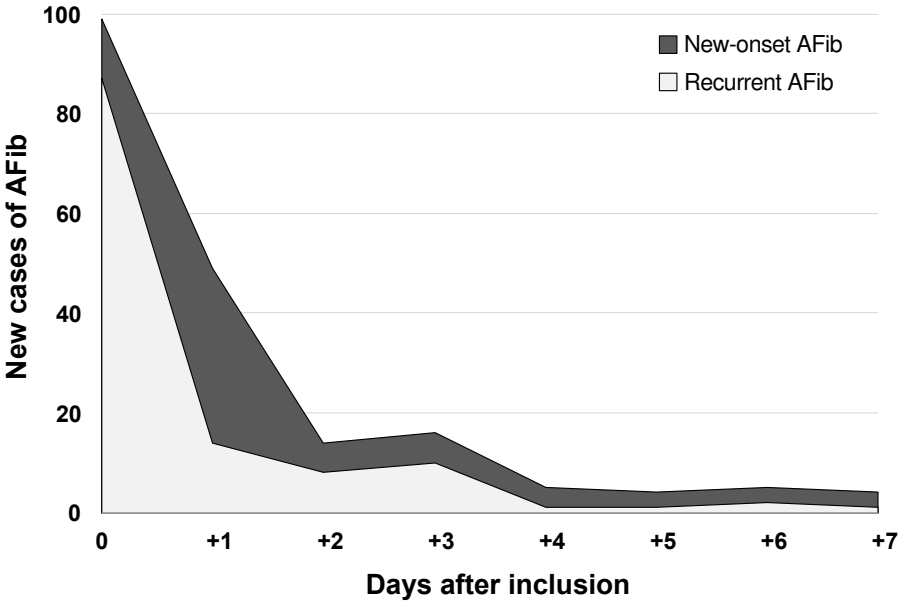
Figures

Figure 1. Flowchart of the study population



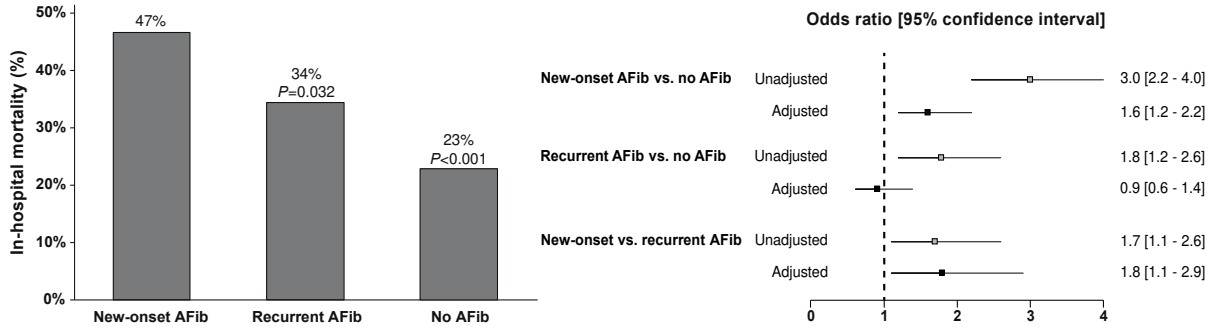
Legend: AFib atrial fibrillation, ICU intensive care unit

Figure 2. Incidence of new cases of atrial fibrillation after study inclusion



Legend: AFib atrial fibrillation

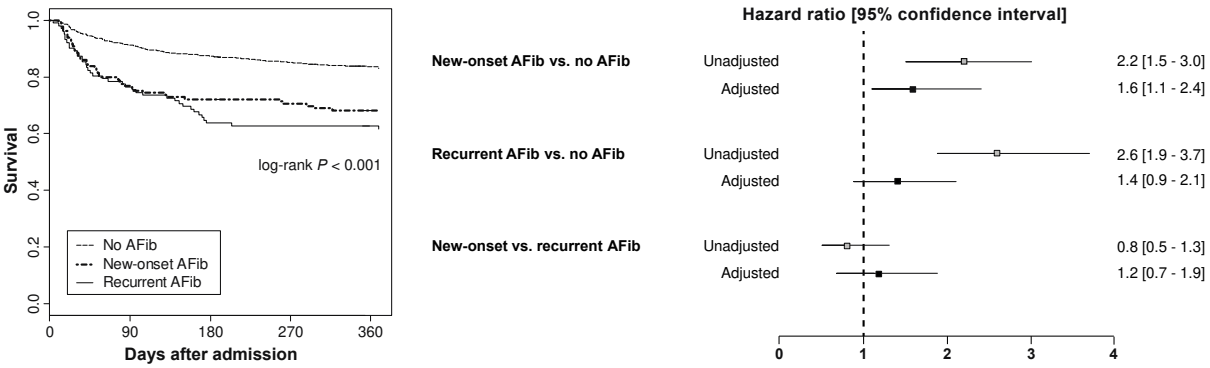
Figure 3. In-hospital mortality according to occurrence of AFib during ICU stay



Legend: Reported P-values refer to comparisons with the new-onset AFib group. Adjustment performed for age, gender, SAPS II, treatment with inotropes or vasopressors at inclusion, serum lactate level at inclusion, high-sensitive troponin I at inclusion, BNP at inclusion

AFib atrial fibrillation - BNP B-type natriuretic peptide - SAPS simplified acute physiology score

Figure 4. Long-term outcome of ICU survivors (n=1464) according to occurrence of AFib during ICU stay



Legend: Adjustment performed for age, Charlson comorbidity index, loss of autonomy, severe valve disease or prior valve surgery, chronic renal disease, peripheral vascular disease, recent malignant tumors, red blood cell transfusion during ICU stay, length of ICU stay > 20 days, systolic blood pressure at ICU discharge, body temperature at ICU discharge < 37°C, leucocytes at ICU discharge > 20 G/L, platelets at ICU discharge < 10 G/L, total serum protein at ICU discharge < 60 g/L.

AFib atrial fibrillation - CRP C-reactive protein - ICU intensive care unit